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Progress and setbacks: The two faces of technology emergence

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ABSTRACT

Emerging technologies are an important driver of economic growth. However, the process of their emergence may not only be characterized by technological progress but also by setbacks. We offer a perspective on technology emergence that explicitly incorporates setbacks into the technology's evolution and explains how industry participants may react to setbacks in emerging technologies. We consider that the locus of innovation in an emerging technology encompasses different types of organizations (industry incumbents, entrants and public research organizations (PROs)) who operate in different institutional environments, and explore how these organizations react to setbacks in terms of their R&D efforts. We study two emerging biotechnologies in the global pharmaceutical industry - gene therapy (GT) and monoclonal antibodies (mAbs). The emergence of both technologies during the 1990s was punctuated by periods of setbacks. We observe a gradual increase in industry participants' R&D efforts during periods of progress and a significant decline in those efforts immediately following setbacks. The decline in R&D efforts was more pronounced for firms than for PROs as well as for those firms that were listed on the stock market in contrast to those that were privately financed. Finally, the decline in R&D efforts towards GT was much more pronounced for those organizations located in countries with high capital fluidity. These findings reinforce that organizational and institutional characteristics that are typically attributed to facilitate R&D efforts towards emerging technologies do induce greater levels of those efforts during periods of progress. However, the same characteristics are also associated with a significant decline in R&D efforts immediately following periods of setbacks. Overall, the study illustrates how setbacks reconfigure the locus of innovation in emerging technologies and offers a richer perspective on technology emergence as one that is rooted in both progress and setbacks. In so doing, it highlights the challenges of sustaining technological progress and offers guidance for policy.

1. Introduction

The emergence of new technologies has long been recognised as an important driver of economic growth (Dosi, 1982; Freeman and Soete, 1997). When studying emerging technologies, the emphasis in the technology management literature has been on their origins (e.g., Basalla, 1988; Jensen and Thursby, 2001; Levinthal, 1998; Vincenti, 1984); their trajectory of progress (e.g., Anderson and Tushman, 1990; Dosi, 1982; Foster, 1986; Sahal, 1985); and their impact on industry participants (e.g., Christensen and Rosenbloom, 1995; Kapoor and Klueter, 2015). The general approach deployed within the technology management literature has been to characterize the process of emergence of new technologies as a smooth, cumulative advance, and how their successful emergence interacted with the efforts and outcomes of industry participants. While this approach has yielded valuable insights, it has underemphasized the fact that the evolution of emerging technologies does not adhere to a smooth pattern of cumulative progress but is, in fact, often disorderly and punctuated by episodes of setbacks (Freeman and Soete, 1997; Kline and Rosenberg, 1986; Nelson, 1964; Rotolo et al., 2015).

A setback represents a technological challenge that is revealed *posteriori* as industry participants exert efforts towards the technological advance, checking or reversing the initial progress in an emerging technology.[1] Setbacks are a relatively common feature of technology emergence, as has been made evident by the cases of ballpoint pens (Cooper and Smith, 1992), biogas (Geels and Raven, 2006), electric cars (Garud and Gehman, 2012), fuel cells (Bakker, 2010) and semiconductor lithography equipment (Adner and Kapoor, 2016). However,

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[1] Our definition of setback is consistent with English dictionaries, according to which a setback is "a reversal or check in progress" (Oxford), or is "a reversal, check, or interruption in progress" (Collins).

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studies of technological change and industry evolution have not systematically explored how industry participants react to those setbacks.

Our objective in this study is to offer a perspective on technology emergence that incorporates setbacks into the technology's evolution and, more importantly, to explain how industry participants may react to setbacks in emerging technologies. Organizations and capital providers pursuing the emerging technology, regardless of whether they were or were not directly involved in the setback, face the choice of either continuing to do so or to reallocate resources to alternative technologies and activities. We expect that a setback in an emerging technology will, in general, result in the withdrawal of resources from that technology. However, that withdrawal may not be uniformly distributed across industry participants, who depend on different types of resource providers with distinct motivations (Ferreira et al., 2014; Hopkins et al., 2013; Nelson, 1986; Salter and Martin, 2001), and who may operate in different types of environments in terms of the ease with which capital can flow in and out of opportunities (Bartholomew, 1997; Brown et al., 2009; Kaiser and Prange, 2004). While capital fluidity can help attract investments in an emerging technology (Bartholomew, 1997; Beck et al., 2000; Li and Zahra, 2012), in the face of setbacks, it can also trigger the flight of capital away from that technology.

Even within an institutional environment, there are different types of industry participants who vary in terms of both their motivations for pursuing emerging technologies and their resource dependencies. Extant research has emphasized that public research organizations (PROs) play an important originating role for emerging technologies through new discoveries, while established firms and entrants play a more important role in subsequent development and commercialization of those technologies (Cohen et al., 2002; Powell et al., 1996; Rothaermel, 2001; Zucker et al., 1998). However, while firms and their resource providers are motivated by economic returns, PROs are motivated by knowledge production and social rate of return (Arrow, 1962; Nelson, 1986). Moreover, firms are subject to greater short-term pressures from their resource providers to generate economic returns (Hopkins et al., 2013; Martin and Scott, 2000; Salter and Martin, 2001). These pressures tend to be higher in those firms relying on capital markets than for those that are privately financed (Aggarwal and Hsu, 2013; Boot et al., 2006; Ferreira et al., 2014). We explore the ways in which such differences across institutional environments and among these different types of industry participants impact their R&D efforts towards an emerging technology in the face of setbacks.

The context for the study is the global pharmaceutical industry from the early 1980s to 2015. During this period, the industry witnessed the emergence of two new biotechnologies that gathered significant interest: gene therapy (GT) and monoclonal antibodies (mAbs). Both technologies promised superior biology-based therapeutic alternatives to traditional chemistry-based treatments. As a result, the two technologies attracted substantial R&D investments by pharmaceutical and biotech firms as well as PROs worldwide (Verma and Somia, 1997). However, the emergence of both technologies has been punctuated by periods of setbacks, which have raised doubts about their scientific progress and overall technological viability as a therapeutic approach (Kapoor et al., 2017; Marks, 2012). Hence, our context presents an important and relevant research setting in which we observe technology emergence, not only as a stylized representation of cumulative progress, but also as one in which technology emergence entails both progress and setbacks.

The study is based on fieldwork conducted between 2012 and 2014. Over this period, we interviewed 14 industry experts who were employed by biotechnology entrants, pharmaceutical firms and public research organizations, many of whom had substantial knowledge and experience with respect to the focal technologies. 12 of the interviewees held a PhD in either biology or chemistry, and 9 of the interviewees had experience with both mAbs and gene therapy. We also attended industry conferences and read through hundreds of trade and scientific publications to understand the challenges that have risen during the emergence of the two technologies. We supplemented the insights that we gained with respect to progress and setbacks through our fieldwork with a novel approach that leverages archival textual data to evaluate historical trends in the positive and negative sentiments towards an emerging technology (Taboada et al., 2011). This allowed us to clearly delineate periods of progress and setbacks in the two emerging biotechnologies. Given that patents are a valid proxy for R&D efforts in the pharmaceutical industry (Griliches, 1990; Kaplan et al., 2003; Lim, 2004), we evaluated industry participants` reactions to setbacks by observing their patenting behavior within the two technologies.

Overall, the patenting patterns suggest a gradual increase in industry participants' R&D efforts during periods of progress, and a significant decline in those efforts immediately following periods of setbacks. In comparing the responses of different types of participants to setbacks, the decline in R&D efforts was more pronounced for pharmaceutical incumbents than for PROs for both GT and mAbs, and more pronounced for biotechnology entrants than for PROs for GT. In both emerging technologies, the decline in R&D efforts following setbacks was greater in firms that were listed on the stock market than for those that were privately financed. Finally, the decline in R&D efforts towards GT was much more pronounced for those organizations located in countries where formal institutions create an environment of high capital fluidity.

These findings showcase how different types of industry participants embedded in institutional environments react to setbacks and emphasize the importance of incorporating setbacks as a key evolutionary feature of emerging technologies. In so doing, they help identify several counterintuitive patterns as several institutional and organizational factors that are typically presumed to fuel R&D efforts in emerging technologies do so only during periods of progress but not during periods of setbacks. For example, while the ease of capital flows is often presumed to be a positive feature of the institutional environment with respect to the pursuit of emerging technologies (Bartholomew, 1997; Kaiser and Prange, 2004), we show that such an environment may have unintended side effects because capital can also be withdrawn more easily following setbacks. Similarly, firms in R&D intensive industries often list themselves on the stock market to gain access to resources and facilitate the pursuit of emerging technologies (Boot et al., 2006; DeCarolis and Deeds, 1999). However, we show that these firms are also those with the most precipitous decline in R&D efforts following setbacks, suggesting that they may be subjected to greater scrutiny and pressures from their resource providers. Finally, while prior research has examined PROs undertaking an important originating role through new discoveries (Zucker et al., 1998), we illustrate that they may also have an important sustaining role in the face of setbacks as firms withdraw or reallocate their R&D efforts towards alternative technologies.

The study has important implications for public policy, in terms of both the characteristics of the institutional environment and the funding for public research. For example, policymakers advocating for free flow of capital and structuring the institutional environment accordingly may need to consider the possibility of setbacks triggering the flight of capital away from their regions. However, they may be able to offset the capital drain with greater support for public research, not only for initiating new technological domains but also for continuing research during periods of setbacks, and by encouraging collaboration between firms and public research organizations.

2. Progress and setbacks in emerging technologies

A stylized description of the trajectory of progress for an emerging technology is that there is slow but gradual improvement in the technology's performance, as reflected through a canonical S-shaped pattern (e.g., Dosi, 1982; Foster, 1986; Henderson, 1995; Sahal, 1985). The

focal technology eventually outperforms existing technologies and achieves market dominance, which continues until it is challenged by newer emerging technologies (Anderson and Tushman, 1990). Underlying this pattern of progress are efforts by industry participants who allocate resources towards an emerging technology in the hope of its successful commercialization.

However, in many cases, progress within an emerging technology does not adhere to a smooth pattern of cumulative improvement. Rather, the trajectory of progress can be punctuated by setbacks (Freeman and Soete, 1997; Kline and Rosenberg, 1986; Nelson, 1964; Rotolo et al., 2015). A setback represents a technological challenge that is revealed *posteriori*, checking or reversing the initial progress in an emerging technology (Rosenberg, 1996). For example, Kline and Rosenberg (1986) alluded to the notion of setbacks in emerging technologies, drawing on the premise that technological innovation usually does not adhere to smooth, linear or well-behaved patterns but is largely complex and somewhat disorderly, with shortcomings and failures being common features of the innovation process. Consistent with this perspective, there is also a narrative around hype in emerging technologies that is premised on inflated expectations, often set by actors to attract resources, that fail to materialize in the short-term (Garud and Gehman, 2012; Rotolo et al., 2015).[2]

In many cases, a setback is not a single discrete event but rather manifests through a series of events that occur over a relatively short period during the technology's evolution. During this period of setbacks, as many industry participants pursue the emerging technology, new information about the technology is revealed which points to significant technological challenges to all industry participants, not just to those who are directly involved in the setback. For example, the emergence of biogas plants in the early 1980s held substantial promise as an alternative source of energy. Despite significant efforts by industry participants, however, initial progress in biogas was checked by a period of setbacks. Technical breakdowns were a common feature in the early varieties of biogas plants as pumps suffered from blockages; digesters worked poorly; and engines and transportation pipes were corroded due to unanticipated amounts of hydrogen sulphide found within biogas (Geels and Raven, 2006). This led to serious doubts among the suppliers and the farmers about the viability of the technology in the short-term.

In a similar vein, the emergence of hydrogen fuel cells for cars in the late 1990s was also characterized by setbacks. A broad set of industry participants in the auto industry pursued this emerging technology as a lower-cost and environmentally friendly alternative to gasoline-powered combustion engines. However, in the mid-2000s, the initial excitement was followed by a period of setbacks as the low density of hydrogen gas limited the amount of hydrogen that could be stored in a vehicle, and avoiding impurities in producing hydrogen to prevent unintended electrochemical reactions proved to be very costly (Andújar and Segura, 2009; Bakker, 2010).[3] Similar episodes of setbacks in emerging technologies have been documented in the cases of ballpoint pens, steam engine-powered ships, and semiconductor lithography (Adner and Kapoor, 2016; Cooper and Smith, 1992; Geels, 2002).

As these examples illustrate, setbacks represent an important and common feature of the evolution of an emerging technology. However, this feature and how different types of industry participants react to those setbacks have been underexplored within the technology management literature. Industry participants not only exert efforts during periods of anticipated progress but also react during periods of setbacks. Setbacks can attenuate expectations regarding the emerging technology, at least in the short-term, but they also necessitate significant additional effort for the potential of the technology to materialize in the long-term. Accordingly, understanding the evolution of emerging technologies requires recognition of not only how industry participants continue along the trajectory of progress but also of how they react to setbacks. Note that our intent in this study is not to suggest that expending R&D efforts following the setback is always a desirable course of action. It is possible that the challenges during setbacks may be too severe for the technology to achieve its expected potential, and when reducing efforts or even abandonment may indeed be an ex post "rational" choice. However, given that many emerging technologies do successfully evolve after facing significant setbacks, a boundedly rational choice in the face of uncertainty may still entail pursuit of the emerging technology, at least in the short-term.

3. R&D efforts in the face of setbacks in an emerging technology

Resources expended towards an emerging technology are determined based on the expectations of progress by industry participants and their external resource providers such as customers, investors or government authorities (Benner, 2010; Christensen and Rosenbloom, 1995; Cooper and Smith, 1992; Geels, 2004). As the technology improves, it allows industry participants to garner additional support and resources. In contrast, setbacks in an emerging technology increase uncertainty as progress becomes more difficult or success less likely, leading external resource providers to adjust their expectations downward. Expectations are also adjusted as a technology experiencing setbacks requires additional and more than expected capital to progress. For resource providers, such an increase in uncertainty leads to a higher required rate of return, which lowers their propensity to support investments in the emerging technology (Gompers and Lerner, 2004; Hopkins et al., 2013). Relatedly, following setbacks, resource providers may actively exert pressure on industry participants to discontinue investments in an emerging technology (Bushee, 1998).

Setbacks can also shape the flow of resources within an organization because they tend to weaken those coalitions in favor of the focal emerging technology as they must adjust expectations and will most likely fail to attain previously set performance goals (Bower, 1970; Burgelman, 1994). Resource commitments are influenced by internal expectations regarding the potential of future performance improvements and the possible commercialization success of an emerging technology. Setbacks will reduce these expectations, hence reducing the willingness of organizations to pursue the technology. Simultaneously, setbacks increase the relative attractiveness of alternative technologies to which resources can be allocated. Indeed, organizations encountering negative feedback when pursuing uncertain technologies often allocate their resources to better understood and more certain paths of actions (Denrell and March 2001). For example, when confronted with setbacks in the emergence of new lithography technology in the semiconductor industry, a broad set of industry participants engaged in a "last resort" effort and allocated substantial resources to support and extend the well-understood and prevailing technology (Adner and Kapoor, 2016).

In summary, setbacks in an emerging technology will increase both the pressure and scrutiny from external resource providers and will also generate internal impetus towards reallocating resources towards alternative initiatives. However, these pressures and the nature of scrutiny may not be the same for all industry participants; hence, those participants may vary with respect to how they respond to setbacks. We explore these differences by considering different types of industry participants – incumbents, entrants and public research organizations – who may be governed by distinct motivations, and who may be embedded in institutional environments with varying levels of capital fluidity.

[2] Recent research has shed light on the theoretical and empirical inconsistencies in the literature around hype (Dedehayir & Steinert, 2016).

[3] The technical challenges for the storage of hydrogen gas also raised concerns regarding the infrastructure required in the form of hydrogen gas stations.

3.1. Institutional environment in terms of capital fluidity

An important characteristic of the institutional environment with respect to R&D efforts in emerging technologies is the ease with which capital can flow across opportunities within regions or countries (Arregle et al., 2013; Freeman, 1995). Economic institutions play an key role in facilitating capital flows from both within and from outside countries (Levine, 1998; Martin and Sunley, 1998). Regions like "Silicon Valley" or "Route 128″, as well as countries such as Sweden and the UK, are well-known for their highly developed capital markets and formal economic institutions (e.g., effective role of banks, protection of investment by governments) to support the efficient flow of capital across the different technological and entrepreneurial opportunities (Beck et al., 2000; Lerner and Tåg, 2013; Li and Zahra, 2012; Saxenian, 1994). In the context of setbacks, such "efficient" movement of capital may however have unintended side effects for R&D efforts in the emerging technology.

A high level of capital fluidity makes it easier to attract investments in an emerging technology but can also make it easier for that capital to be withdrawn in the face of setbacks. In particular, the presence of effective formal institutions can help structure and facilitate economic exchanges but can also facilitate rapid resource outflows (Gompers and Lerner, 2003). In a similar vein, extant research has associated the ease of capital flows in regions and countries with "speculative" type of financing and venture capital financing, fueling investments but also accelerating outflows in the face of shocks or crises (Bartholomew, 1997; Gompers and Lerner, 2003; Ranciere et al., 2008). Moreover, the flow of capital also tends to closely correspond to the flow of information (Brown et al., 2009). Information following setbacks will be more readily diffused in an institutional environment with high level of capital fluidity as formal institutions are effective in disseminating that information. Investors and capital providers in such environments are thus more likely to reduce their level of investment in the face of setbacks, which negatively shapes R&D efforts towards the emerging technology.

3.2. Types of industry participants (PROs, incumbents, entrants)

A broad range of industry participants, including public research organizations, entrants and incumbent firms, contribute to the advancement of emerging technologies (Kapoor and McGrath, 2014; Powell et al., 1996; Rosenberg and Nelson, 1994). Extant research has emphasized the role of public research organizations in the initiation and origination of research in emerging technologies, while established firms and entrants are considered important drivers for the subsequent development and commercialization of new technologies (Cohen et al., 2002; Deeds et al., 2000; Jiang et al., 2011; Rothaermel, 2001). To finance their investments, firms, particularly those in R&D intensive industries, list themselves on the stock market, which can provide access to larger equity-based financing and reduce the overall cost of capital for needed investments (Boot et al., 2006; DeCarolis and Deeds, 1999; Stuart et al., 1999). At the same time, different industry participants are subject to distinct motivations and resource dependencies, which can shape their response to setbacks.

In contrast to incumbents and entrants, PROs focus on social rates of returns — i.e., how society can benefit as a whole — and expected economic rates of return for publicly funded research tend to be lower than for R&D initiatives by firms (Salter and Martin, 2001). As a result, R&D budgets in PROs are more immune to external market pressures than are those of firms (Tolbert, 1985). Indeed, PROs have been characterized as being more resilient and stabilizing in highly volatile technological fields (Owen-Smith and Powell, 2004). This will make it more likely that, relative to firms, PROs will sustain their R&D efforts in the face of a setback in an emerging technology.

While a setback can check or reverse progress in an emerging technology, it can also reveal challenging problems. Solving such problems is an important domain of researchers in PROs, who are driven by "curiosity-oriented research", i.e., the motivation to understand why the setback happened and to identify potential solutions (Salter and Martin, 2001; Zucker et al., 1998). Furthermore, in anticipation of the withdrawal of efforts by firms from an emerging technology subject to a setback, PROs may deliberately compensate for such underinvestment by increasing their commitment to the focal technology (Godoe, 2000; Martin and Scott, 2000). This is consistent with the idea that public research addresses "market failure" by investing in areas in which firms have little incentive to do so due to appropriation concerns or technological uncertainty (Arrow, 1962; Nelson, 1959). In summary, while there might be a general decline in R&D efforts by all industry participants following a setback, we expect that this decline will be much more pronounced for industry incumbents and entrants than for PROs.

Within firms, there is also heterogeneity with respect to resource dependencies between those that are listed on the stock market and those that are privately financed (Boot et al., 2006; Ferreira et al., 2014). In general, financing by the stock market can be beneficial for firms to accelerate their pursuit in emerging technologies. For example, Hopkins et al. (2013) showed that firms listed on the stock market were more likely to achieve critical R&D milestones than those that were financed through alternative means. At the same time, firms listed on the stock market tend to have greater separation between ownership and control, subjecting the firms' managers to additional pressures from investors and stock market analysts (Benner, 2010; Bushee, 1998). These pressures are exacerbated as firms listed on the stock market are also required to immediately disclose important information (Aggarwal and Hsu, 2013; Ferreira et al., 2014).

Another difference between privately financed firms and those listed on the stock market is the time horizon that firms consider appropriate for their innovative projects. Firms listed on the stock market tend to allocate resources to conform to short-term earnings expectations as managers must pay attention to their firms' stock value and quarterly reporting (Aggarwal and Hsu, 2013; Manso, 2011; Noda and Bower, 1996). This short-term orientation is reinforced by the way quarterly earnings reports are scrutinized by financial analysts. In contrast, firms that remain privately financed have been shown to take a longer-term approach to their investment decisions and, in general, are more willing to go against the general perceptions of financial markets (Boot et al., 2006). Consistent with those arguments, Hopkins and colleagues (2013) observed that, following accounting scandals and disappointing failures in the UK biotech industry, VC financing and alternative financing became relatively more important sources of capital, while financing through stock markets declined.

As compared to publicly listed firms, privately financed firms are more likely to be shielded from pressures from their resource providers during the period of setbacks and would be able to take a longer-term orientation with respect to their R&D investments. Accordingly, we expect the decline in R&D efforts following a setback to be lower for privately financed firms than for firms listed on the stock market.

Next, we offer an empirical exploration of industry participants` R&D efforts towards two distinct emerging biotechnologies, highlighting the periods of setbacks and how the different types of actors, embedded in different institutional environments, responded to setbacks.

4. Emerging technologies in the global pharmaceutical industry

The inception of biotechnology in the 1980s has been characterized as an important and radical technological change, with a shift from chemistry-based to biology-based therapeutics. The late 1980s saw the emergence of new biotechnologies, drawing on genetic engineering. We focus on the evolution of two major biotechnologies that gained substantial attention during this period – monoclonal antibodies (mAbs) and gene therapy (GT).

Antibodies are produced by the human immune system in response

to foreign proteins (antigens) that are the causes of illnesses and diseases. Antibodies-based treatments promised several advantages over traditional chemistry-based treatments; namely, they are much more specific to an antigen, have a lower risk of toxicity, and can address a wider range of biological mechanisms, with scientists referring to them as "magic bullets." Gene therapy offered a treatment for inherited diseases caused by defective genes. The therapy entails inserting genetic material into human cells to regulate or repair their functionality (Wirth et al., 2013). This led to substantial enthusiasm as treatments could provide a permanent cure for a broad range of inherited diseases and with greater opportunities for personalized medicine (Friedmann, 1992; Verma and Somia, 1997). As we detail below, the evolution of mAbs and GT did not follow a trajectory of cumulative progress but instead included periods of both progress and setbacks.

4.1. Emergence of monoclonal antibodies (mAbs)[4]

In the late 1980s, mAbs were initially derived from mice and were called murine mAbs. These antibodies faced challenges with respect to their therapeutic effectiveness and the side effects associated with patients' immune systems rejecting murine-based cells. Scientists attempted to overcome these problems by using less murine and more human content over time. Accordingly, several types of mAbs with greater human content were developed (i.e., chimeric, humanized and fully human antibodies). The early development of these antibodies and the initial results were heralded as significant progress in the technology as they were less likely to cause an adverse immune response and had the potential to be more effective than those based on murine antibodies (Marks, 2012). However, at the start of the 1990s, out of 16 major clinical candidates, 15 did not achieve clinical success because of limited efficacy, leading to major disappointments with respect to the promise of mAbs (Dillman, 1989; Nelson et al., 2010). Indeed, discussing this episode in the evolution of mAbs, historian Lara Marks (Marks, 2015:preface) emphasized that "much of the optimism surrounding mAb therapeutics of the early 1980s had dissipated at the end of the decade" and that "by the early 1990s, many had become despondent about its [mAbs] therapeutic potential."

In 1991, one novel chimeric mAb, Centoxin, developed by a biotechnology entrant, Centocor, was approved in Europe for the treatment of sepsis. However, the treatment was under severe scrutiny by the medical community and regulators, who challenged the clinical results and warned of possible side effects (Baumgartner et al., 1990; Marks, 2015). Indeed, in 1992, the US Food and Drug Administration (FDA) demanded additional data for Centoxin and subsequently denied its approval. By the end of 1992, Centoxin also had to be withdrawn in Europe as data revealed unexpectedly high mortality rates among certain group of patients. In the same year, another murine mAb, Edobacomab, developed by a biotechnology firm Xoma, also failed to achieve clinical approval due to lack of efficacy.[5] The string of disappointing clinical outcomes constituted a period of setbacks during the evolution of mAbs, with significant concerns being expressed by industry participants and the popular press about future viability of mAbs, along with several major firms losing faith in mAbs as a therapy (Marks, 2015:149).

This initial period of setbacks, however, was quickly followed by encouraging news. As early as 1993, another chimeric mAbs by Centocor, ReoPro, achieved positive clinical results and, in 1994, the drug was approved in both the US and the EU. This was important for the development of mAbs overall. For example, Marks (2015: 159) noted that "ReoPro's approval not only marked a critical milestone for Centocor, but placed mAbs firmly on the therapeutic map." Following this period, humanized and fully human mAbs also made additional progress and proved to be less invasive, more effective and, in general, safer than many prevailing treatments (Nelson et al., 2010). As a result, mAbs and, in particular, fully human mAbs became the preferred treatments in many therapeutic areas during the 2000s. In 2002, just three years after its approval, Humira, a fully human mAb used in the treatment of rheumatoid arthritis, became the first treatment with over $1Billion in worldwide sales; a decade later, five out of the top 10 best-selling drugs worldwide were mAbs. As this brief historical account suggests, the emergence of mAbs entailed a period of initial progress and technological advance, punctuated by a short period of setbacks which were then followed by a sustained period of progress and successful commercialization.

4.2. Emergence of gene therapy (GT)

During the mid-1980s, gene therapy initially focused on ex-vivo approaches in which cells would be corrected by replacing their genetic material. The therapy entailed extracting the affected cells from the patients, correcting the cell`s genetic composition through a vector (a delivery mechanism to transport corrected genes into cells), and then re-inserting the corrected cells into the human body. Initial laboratory tests to insert foreign gene into stem cells were highly encouraging (Wirth et al., 2013). In the late 1980s, scientists carried out experiments to establish that gene therapy would be safe and effective when used to treat certain types of cancer (Rosenberg et al., 1990). Between 1988 and 1990, the first clinical protocols to introduce a foreign gene into humans were approved and the first clinical trial for gene therapy was conducted, treating a patient with a severe type of immunodeficiency, which was followed in 1993 by treating newborn infants with the same condition (Cavazzana-Calvo et al., 2004). While these initial trials were deemed successful and suggested a broad range of therapeutic applications for gene therapy, they also revealed that the ex-vivo approach was limited in its efficacy (i.e., the ability to fully cure the disease), owing to the limited ability of corrected cells to reach the affected parts in the human body (Friedmann, 1992; Smith, 1999). This led scientists in the mid-1990s to explore an in-vivo approach, whereby the genetic material is directly inserted into the human body through a vector. During this period, several novel vectors were identified and developed, including certain types of viruses. In 2000, a paper published in *Science* marked the first reported definitive cure through viral vector gene therapy of patients suffering from severe combined immunodeficiency (SCID) (Cavazzana-Calvo et al., 2000).

At the turn of the century and despite an initial period of progress, GT was subject to a period of significant setbacks. In particular, the in-vivo approach using viral vectors to deliver the genetic material caused severe side effects for patients (Hoag, 2005). In late 1999, one patient undergoing a gene therapy clinical trial using a viral vector unexpectedly died due to an adverse reaction, leading to heightened scrutiny by regulators and concerns about the future of that form of therapy (Hollon, 2000). These concerns were further exacerbated as children reported to be the first ever cases of gene therapy's success using viral vectors in 2000 subsequently developed a form of cancer during 2001–2002. In fact, in 2002, these concerns led the FDA to temporarily halt several gene therapy clinical trials (Cavazzana-Calvo et al., 2004; Thomas et al., 2003). During this period, industry observers raised serious doubts about gene therapy's safety and the scientific community recognized the need to better understand the science behind that form of treatment (Williams and Baum, 2004; Wilson, 2014). Many of the well-known entrants in gene therapy such

[4] We are very grateful to the editor and the reviewers for helping us develop a richer understanding of the history of mAbs in terms of both progress and setbacks.

[5] Xoma's Edobacomab had been in a race with Centocor's Centoxin for gaining approval to treat sepsis in the US. This race to achieve approval, in conjunction with an ongoing patent dispute between the two firms, likely made existing problems in the clinical results and the issues with the design of the clinical trials surrounding those mAbs more visible (Marks, 2015).

as Introgen Therapeutics and Vical exited or reduced their R&D efforts in GT during this period, while many pharmaceutical firms such as Merck and Pfizer substantially downsized or divested their GT R&D units.

Following this period of setbacks, different variants of vectors such as non-viral vectors and gene therapy, including RNA interference or Antisense, were explored (Hoag, 2005). In April 2005, new gene therapies treating SCID were tested, which did not have the same side effects as those using viral vectors. Over the following decade, many of the underlying challenges that surfaced during the period of setbacks were resolved. In 2012, the European Medicines Agency recommended the first gene therapy (Glybera) that addressed a rare genetic disease for approval (Wirth et al., 2013). Subsequently, improvements were also made to ex-vivo gene therapy, with the resulting therapies (CAR-T) finding success through clinical development and product approvals in both Europe and the US.[6] As the above account suggests, the emergence of gene therapy was characterized by an initial trajectory of progress, which was punctuated by a period of setbacks from 2000 to 2002, followed by a prolonged period of slow, cumulative progress.

5. Analysis

5.1. Examining progress and setbacks in mAbs and GT through sentiment analysis

We explored the utility of sentiment analysis for the purpose of evaluating progress and setbacks in emerging technologies, and how it corresponds to our understanding of the history of mAbs and GT. Sentiment analysis is a relatively new quantitative approach that leverages text data to extract subjectivity and polarity from text (Taboada et al., 2011). We used sentiment analysis to assess the positive and negative sentiments with respect to GT and mAbs expressed in the popular press and the scientific journals. We expect that a higher proportion of negative sentiments would correspond to periods of setbacks.

We used a keyword-based approach to extract all news articles mentioning the two technologies in major English-language newspapers: *The New York Times, The Wall Street Journal, The Washington Post, Time, The Financial Times* and *The Guardian*. We supplemented these popular press articles with articles from the major journals in health sciences that cover emerging biotechnologies: *Nature, Nature Biotechnology* and *The Nature Drug Review*.[7] We identified over 7000 news articles, with about 60% of those articles mentioning gene therapy and about 40% mentioning monoclonal antibodies. We then analyzed the individual articles using Wordstat (7.0) based on Wordstat's proprietary sentiment dictionary, which classifies words according to positive and negative sentiments (Pollach, 2011). We excluded several words from the analysis that were being categorized as positive or negative based on the dictionary (e.g., cancer, disease, infectious) but that were "neutral" from a perspective of evolution of the biotechnology. On average, an article had 804 words, of which 82 were categorized as either a positive or a negative sentiment.

We captured the overall sentiment underling the evolution of mAbs and GT by following a well-established approach within the field of computational linguistics (Taboada et al., 2011). Specifically, we divided the total number of negative words by the total number of positive words for each article (i.e., the sentiment score), and then averaged the sentiment scores across articles on a yearly basis.[8] In general, higher values of sentiment scores represent more negative sentiment relative to positive sentiment.

Figs. 1 and 2 show the average sentiment scores over time for mAbs and GT respectively. The pattern of sentiment scores is striking across both technologies, and corroborates well with the general episodes of progress and setbacks that we discussed above. The initial periods for both mAbs and GT are associated with generally positive sentiment relative to the negative sentiment. However, the sentiment scores for mAbs dramatically shifted towards those that were much more negative, around the 90th percentile, during 1989–92. This corresponds with the period during which there were several failed clinical trials (Marks, 2015; Nelson et al., 2010). In addition, this period also witnessed an intense patent fight between two promising mAbs start-ups — Centocor and Xoma — which also contributed to the overall negative sentiment surrounding mAbs (Bluestone, 1991).

The gradual transition towards more positive sentiment scores seems to coincide with several clinical successes from mid-1990s onwards, the only exception being the year 2006, in which the sentiment score becomes very high (i.e., very negative). This can be attributed to a major tragedy in a clinical trial, in which six patients suffered multiple organ failures immediately after receiving a monoclonal antibody treatment developed by a startup, TeGenero. This single event received substantial attention, and the adverse reaction of patients was blamed on inadequate preclinical procedures (Sheridan, 2006). However, this episode was much more specific to a single firm and did not represent a technological setback for mAbs overall. This was confirmed by an immediate reversion to more positive sentiment scores in the following years.

Similar to mAbs, the sentiment scores for GT also shifted dramatically towards the negative, but almost ten years later than those for mAbs (i.e., 1999–2002). This period corresponds to the time during which patients undergoing clinical trials suffered from very severe and unexpected side effects, with the FDA going so far as to halt several ongoing gene therapy clinical trials. Following this period, the sentiment scores gradually became more positive. In recent years, the sentiment scores have been among the lowest, reflecting heightened interest and optimism around gene therapy. Hence, sentiment analysis seems to offer a valuable validation of the historical evolution of mAbs and GT in terms of the periods of both progress and setbacks.

5.2. R&D efforts towards monoclonal antibodies and gene therapy

The evolutions of mAbs and GT have been characterized by clear periods of progress punctuated by periods of setbacks. We now explore the responses of different types of industry participants embedded in different institutional environments to those setbacks. An interesting feature of our research design is that the period of setbacks in one technology corresponded to a period of progress in the other. This also helps to contrast the efforts of different types of industry participants embedded in institutional environments with different levels of capital fluidity during periods of both progress and setbacks.

Ideally, it is desirable to observe industry participants' direct R&D investments towards mAbs and GT, but such archival data are not typically available. Instead, we used publicly available information on patent grants, which have been shown to be strongly correlated with R&D efforts, especially in the pharmaceutical industry (Cockburn and Henderson, 1998; Griliches, 1990; Kaplan and Tripsas, 2008; Lim, 2004). Patent data are obtained from Derwent World Patent Index and include all patents filed in major patent offices worldwide. The database also accounts for the fact that organizations may seek patent protection for the same invention in multiple jurisdictions, as well as

[6] The recent developments in gene therapy have led to heightened interest in and optimism about its therapeutic potential, while at the same time spurring debate as to the ethical boundaries of the therapy (Addison & Taylor-Alexander, 2015; Wirth et al., 2013).

[7] These are important outlets in the fields of biotechnology and medicine, with *Nature* and *Nature Biotechnology* having impact factors greater than 40. We included new like articles found in sections such as Commentaries, News, News & Views items, Editorials and Correspondences, with both *Nature* articles and the popular press revealing similar patterns.

[8] We reduced the effect of outliers by winsorizing the sentiment scores on both tails.

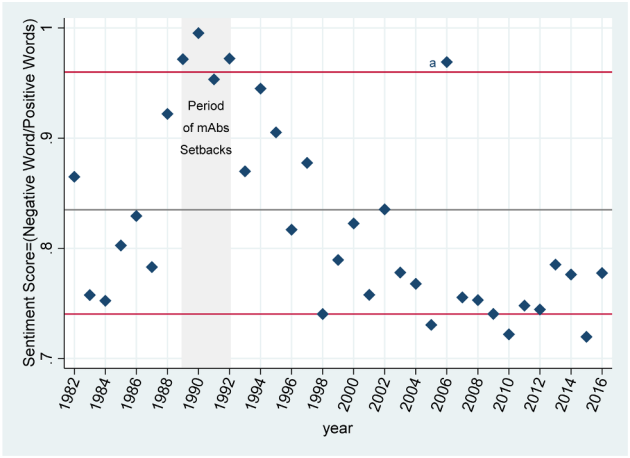

Fig. 1. Sentiment scores - mAbs.
Key Events During the Period of mAbs Setbacks:
1989, mAbs not meeting expectations in a broad range of trials and therapeutic applications (e.g. cancer) (Dillman, 1989; Nelson et al., 2010)
1990, 1991 Efficacy of clinical results in Centoxin challenged, researchers warn of possible side effects (Baumgartner et al., 1990; Marks, 2015).
1992, FDA requests additional data on mAbs in development, Unexpected clinical failures (Xoma - edobacomab, Centocor-Centoxin) (Bluestone, 1992).
a – 2006, multiple organ failures in patients after receiving experimental monoclonal antibody treatment of TeGenero (Sheridan, 2006)

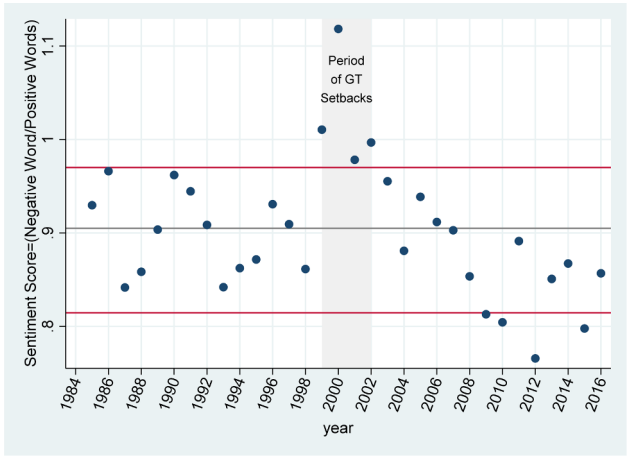

Fig. 2. Sentiment scores - GT.
Key Events During the Period of GT Setbacks:
1999, Death of a patient during a gene therapy clinical trial (Wirth et al., 2013)
2000, 2001 Tightening legislation for the supervision of gene therapy trials in the US (2000) and Europe (2001), continued discussion of possible side-effect following treatments with viral vectors (Donsante et al., 2001; Hollon, 2000; Pfeifer and Verma, 2001; Smaglik, 2000).
2002, Children treated by viral vector gene therapy as part of a clinical trial were reported to develop cancer, Regulators impose temporary hold on selected GT trials (Thomas et al., 2003).

possibly having subsequent revisions to the original patent. A single patent record in the database, labeled as a patent family, often combines multiple patents related to the same invention. Another attractive feature of the Derwent database is its dedicated classification codes for Pharmaceutical patents (category B), which includes dedicated codes for gene therapy (B14-S03: "Gene therapy, general) and for monoclonal antibodies (B04-G21, B04-B04C5: "Monoclonal Antibody") (Kapoor et al., 2017).

Each patent is typically assigned to multiple Derwent codes. An important issue of patents that are assigned to gene therapy code is that several gene-related patents can have many broad claims, captured via multiple Derwent patent codes for a single patent, including the one for gene therapy. This is of particular concern when examining the period of the Human Genome Project (1990–2003), which focused on mapping and understanding thousands of genes within the human body. Accordingly, our data for gene therapy patents could be inflated for this period, and our analysis with respect to the general decline in R&D efforts could be problematic. To mitigate this issue, we consulted a senior scientist at the University of Pennsylvania's School of Medicine, a pioneer in the field of gene therapy, with more than 500 publications and over 100 patent grants. The scientist suggested that we exclude patents associated with genetic primers and probes, as these categories often are connected with "gene patents" but may be only tangentially applicable to gene therapy. Specifically, we excluded about one-third of the patents having the following codes B04E05 (Nucleic Acids: Primers, probes), B11C08E5 (Nucleic acid hybridisation test methods, use of nucleic acid probes), D05H12D1 (DNA, CDNA, RNA non-coding sequences- Primers, probes), B04N02A0E (Genetically Engineered: Complete amino acid sequence given). We found that, on average, the excluded patents had a significantly greater number of assigned codes, suggesting that they may be much broader in their claims, which we would expect for general gene patents. Further, the excluded patents also seemed to belong to a different distribution based on the frequency of codes to which they were assigned. Almost 90% of the excluded patents were assigned to codes with respect to diagnostics, genetic detection and testing, whereas these codes were only assigned to about 40% of patents in the revised sample.

As a final validation of our approach, we compared the Top 20 patentees in the initial sample of all patents assigned to the gene therapy code with those in the revised sample that we intended to use for the analysis. We determined whether each of the Top 20 patentees was actively involved in the preclinical and clinical development of gene therapy.[9] While all patentees in the revised sample were involved in gene therapy development, six of the Top 20 patentees in the initial sample were not. This gave us additional confidence that the revised sample is much more robust to patent-based measurement problems associated with gene therapy.[10]

For the analysis, we use the priority date of the patent application from Derwent to identify the timeframe for R&D efforts. Since our emphasis in the analysis is on organizations with significant R&D efforts, we excluded patents that only had individuals as patent assignees, about 7% of total patents in our dataset, and industry participants only having a single mAbs or GT patent during the period 1982–2015, about 8% of total patents in our dataset. Overall, the analysis was done using a total of 20,972 patent records for mAbs and a total of 19,412 patent records for gene therapy that were applied for between 1982 and 2015. We note that only about 3.4% of all patents were categorized using both GT and mAbs classification codes. This low occurrence is expected because GT and mAbs differ in terms of underlying knowledge domains and clinical mechanisms. In many cases, industry participants will have multiple assignee codes and we were careful to reflect acquisitions and subsidiaries to accurately attribute patents to the correct industry participants.

Fig. 3 contrasts aggregate R&D efforts towards mAbs and GT as measured through total patent counts. As expected, there is an increasing trend in patenting during the initial years. Following the period of setbacks for mAbs (1990–1992) and for GT (2000–02), we observe a significant decline in patenting in the respective technologies.[11] We now explore these patterns in more detail by comparing the

[9] We used ADIS Insights and Pharmaprojects databases to examine the preclinical and clinical development activities (Kapoor & Klueter, 2015).

[10] Detailed results attained from these additional analyses are available from the authors.

[11] It is important to note that the period 2000-2002 also coincided with the bursting of the dot-com bubble. Hence, there is a possibility that the decline in

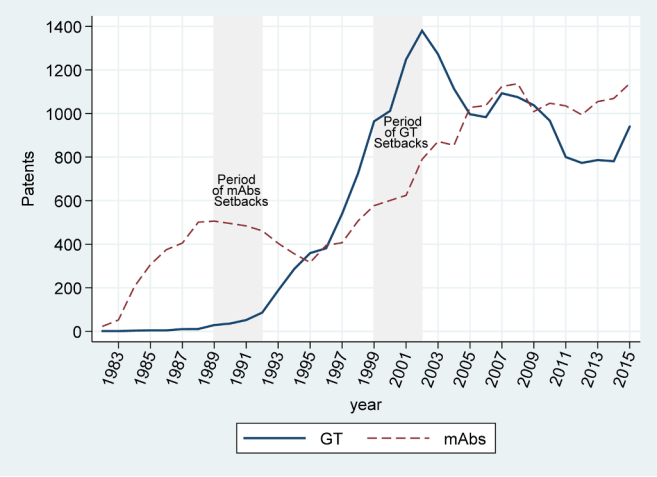

Fig. 3. Overall patent counts in mAbs and GT.

responses of different types of industry participants embedded in several institutional environments.

Identifying institutional environments and industry participants

To explore the role of the institutional environment (capital fluidity), two researchers coded the country of origin for each patent assignee.[12] We then link every country represented in the patent dataset to the investment freedom score of the Index of Economic Freedom, which is provided by the Heritage Foundation (Goerzen and Beamish, 2003; Meyer et al., 2009). According to the Heritage Foundation, the investment freedom score captures the ease with which organizations can "move resources [investment capital] into and out of specific activities, both internally and across the country's borders, without restriction."[13] The score is based on a variety of regulatory restrictions that are typically imposed on investments in the focal country, and that may prevent individuals and firms to move investment capital into and out of specific activities in that country. Each country starts with an ideal score of 100, and points are deducted based on the number and the extent of restrictions and barriers that are imposed. These include a lack of transparency and burdensome bureaucracy for investment within the country; the expropriation of investments without fair compensation; and a lack of basic investment infrastructure or other government policies that indirectly burden the investment process. Accordingly, the score serves as a good proxy for a country's capital fluidity. The patentees come from a total of 44 countries. Countries with lower scores (50 or lower) included China, France and Japan, which are deemed to have formal institutions that restrict flows of capital as compared to countries with significantly higher scores (70 or higher) like Switzerland, the UK, and the US. Overall, the score across the 44 countries ranges between 30 and 90 with an average value of 63.[14]

Industry participants that invested in GT and mAbs included established pharmaceutical incumbents, biotechnology entrants, and public research organizations (PROs). Two researchers independently coded the type of industry participants who patented in GT and mAbs. Consistent with the literature, firms founded before 1976 (the year in which Genentech, the first biotechnology start-up, was founded) were classified as pharmaceutical firms and firms established in or after 1976 were classified as biotechnology entrants (Arora et al., 2009). PROs are all public institutions (e.g., universities or national agencies such as the NIH) and not-for-profit research institutes and foundations. In total, we identified 257 pharmaceutical firms, 2159 biotechnology entrants, and 926 PROs. We also determined whether a firm was privately financed or was listed on the stock market in a given year.[15]

5.2.1. Descriptive trends

Figs. 4 shows aggregate R&D efforts towards mAbs and GT by participants based in countries whose average scores are above and below the overall average in the sample. A high average score implies high capital fluidity in the country. There is an increasing trend in patenting during the initial years, with the trend being much steeper for countries with high capital fluidity. Following the period of setbacks for mAbs (1990–1992) and for GT (2000–02), a significant decline in patenting was also driven by participants in these countries, with the effect being much more precipitous for GT. This pattern suggests that, while high capital fluidity facilitates investments in emerging technologies during a period of progress (Li and Zahra, 2012; Saxenian, 1994), it can also trigger the flight of capital away from emerging technologies following a period of setbacks.

Fig. 5 shows the breakdown of patenting by industry participants (PRO, Pharmaceutical, Biotech). During periods of progress, biotechnology entrants and pharmaceutical incumbents have the largest share of patenting, which is consistent with the idea that firms are an important driver in advancing technologies (Deeds et al., 2000; Hopkins et al., 2013; Jiang et al., 2011). In the face of setbacks, there was a decline in mAbs patenting by pharmaceutical firms during the early 1990s. However, the declines for PROs and biotech firms are much less pronounced. For GT, we observe that, immediately following the period of setbacks (2000–2002), there was a significant decline in patenting by biotechnology entrants and pharmaceutical firms. Interestingly, the decline in the overall patenting was much less pronounced for PROs. These trends highlight the important difference between the pursuit of emerging technologies by for-profit firms and by public research organizations during periods of progress and setbacks.

Fig. 6 plots the patent trend for firms that were privately financed and those that were listed on the stock market.[16] In general, firms listed on the stock market have a larger share of patenting than those that are privately financed, consistent with the idea that firms list on the stock market to finance further investments and grow (Deeds et al., 2000). However, they also exhibit greater decline in patenting following setbacks.

While these patterns reveal important insights as to how different types of industry participants embedded in different institutional environments react to setbacks, we have so far only investigated them on the aggregate level. Next, we offer a statistical analysis of patent trends at the single participant-level to better understand and further validate

(*footnote continued*)
gene therapy investments could be driven by the general economic environment. However, since there was no corresponding decline in mAbs investments, the dot-com crash is unlikely to be the main explanation for the decline in GT investments.

[12] The search included checks about an assignee PROs' country or an assignee firm's headquarters as found in Hoovers, their websites, Google Searches and the WaybackMachine. When no information was found, we used the location of the assignee on the patent. It is possible that firms may undertake R&D in countries external to their home country, especially if they are large, established organizations. However, a significant part of their R&D efforts typically take place within their own countries.

[13] http://www.heritage.org/index/investment-freedom

[14] The investment freedom score is only available from 1995 onwards, and while the score changes slightly over time, the rank ordering of the countries in terms of high and low scores remains rather stable. For the earlier years, 1989-1994 in the sample, we used the 1995 score.

[15] Information regarding whether the firm had gone through an initial public offering (IPO) was retrieved by checking the Evaluate Insights database, their respective websites, and Compustat. Due to data non-availability, we introduce this classification for observations from 1987 onwards.

[16] 34% of biotech entrants and 77% of pharmaceutical firms were listed on the stock market during the period of observations.

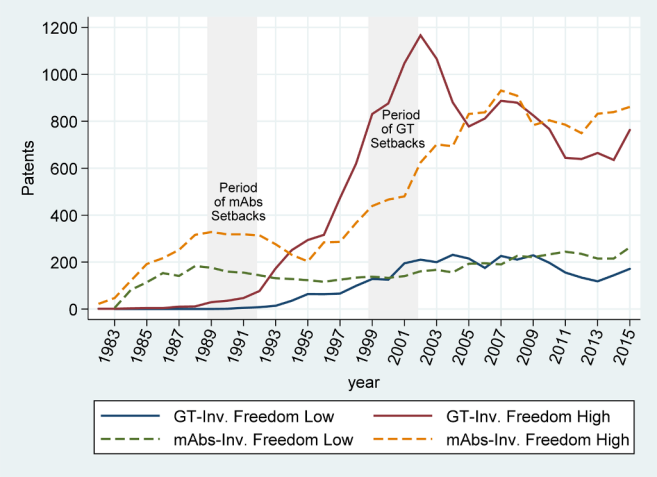

Fig. 4. Patent counts by capital fluidity (Investment Freedom).

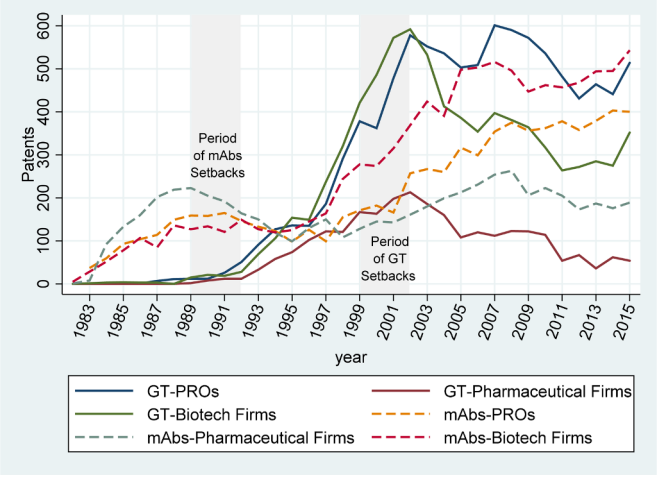

Fig. 5. Patent counts by types of industry participants.

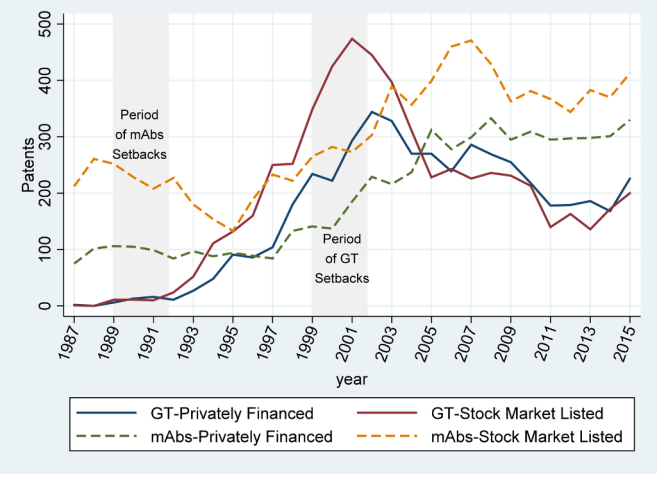

Fig. 6. Patent counts - listed on market vs. privately financed.

the observed patterns.

Statistical analysis (Actor-technology-level)

We construct a panel dataset in which we observe the patent applications and other characteristics for each industry participant before and after the setbacks. We do this over two periods — 1988–1995 (includes period of mAbs setbacks) and 1998–2005 (includes period of GT setbacks). Based on the sentiment analysis (Figs. 1 and 2), we consider the periods after 1992 and 2002 as corresponding to those after the setbacks in mAbs and GT respectively, as sentiment scores became much less negative. We follow each industry participant up to three years following the period of setbacks. The choice of the three-year window is to account for R&D efforts that are more likely to be capturing the response of industry participants to the period of setbacks rather than continuation of R&D projects from previous years or the initiation of new R&D projects at a later period.[17] In our analysis we compare industry participants` patenting rates in GT and mAbs during 1988–1995 and during 1998–2005 respectively. These comparisons help us generate more robust inferences to understand the differences during periods of progress and setbacks, as well as ruling out alternative explanations.

To ensure that our yearly observations represent firms that are active in terms of R&D and have not exited the industry, we identified the first and last patent application (any patent) as the basis for capturing the years in which they were actively conducting R&D.[18] (1988–1995 and 1998–2005). The analysis includes *12,751* industry participants-year observations for mAbs (1459 unique industry participants) and *10,778* assignee-year observations for GT (1330 unique industry participants).

5.2.2. Regression variables and model

The variable *Post-setbacks* takes the value of 1 in the three years following the period of setbacks: 1993–1995 for mAbs and 2003–2005 for GT, and 0 for the other years. The variable *Capital Fluidity* is the yearly score for investment freedom of the Index of Economic Freedom (Goerzen and Beamish, 2003; Meyer et al., 2009), based on the assignee's country of origin. We add industry participants' binary variables for *PROs, Incumbent Pharmaceutical Firms* and *Biotechnology Entrants*, respectively. The variable *Listed* is a binary variable that takes the value of 1 if the focal firm was listed on the stock market and 0 otherwise. To control for the intensity of R&D efforts in mAbs and GT, we include the count of mAbs and GT patents for the prior two years (*Patent History)*. We also control for economic differences across countries using the yearly *Per Capita GDP* of the country of origin of each assignee using data from the Worldbank.[19]

Our dependent variable is the count of patents, and we use count regression models to test our predictions (Allison and Waterman, 2002). We also account for the fact that patenting rates for industry participants may systematically differ during this period for reasons that we may not be able to observe. To account for this possibility, we deploy an actor-level fixed-effects count model. The estimations are derived using a fixed-effects Poisson model deploying a quasi-maximum likelihood estimator (Stata: xtpoisson, fe robust) (Cameron and Trivedi, 2013). Using a negative binomial fixed-effect model yields very similar results.

5.2.3. Descriptive statistics and regression results

Tables 1 and 2 show the summary statistics for the different timeframes investigated in the empirical analysis. The combined samples include industry participants from 33 countries that are active in mAbs and GT. The majority of patenting activity is from industry participants based in the US (55%), followed by Japan (10%) and Germany, the UK and France (about 5% each).

Table 3 shows the regression results. Models 1 through 4 show the baseline effect of all variables. Note that the direct effects of time-invariant variables such as *PROs, Incumbent Pharmaceutical* and *Biotech Entrant* are consumed by the firm fixed effects. The models reveal the

[17] Results are qualitatively similar using the 2-year and 4-year post-setbacks windows.

[18] PROs tend to be active throughout the respective periods.

[19] To eliminate outliers, we winsorize variables for the top 0.1% of all observations for both mAbs and GT.

Table 1
Summary statistics industry participants in GT during mAbs setbacks sample (1988–1995) and GT setbacks sample (1998–2005).

	1988–1995	1	2	3	4	5	6	7	8	9
1	Patents GT	1.00								
2	Patent History	0.32	1.00							
3	Per Capita GDP	0.11	0.12	1.00						
4	Capital Fluidity	0.05	0.03	0.51	1.00					
5	PRO	0.02	0.03	−0.12	0.11	1.00				
6	Incumbent	−0.04	0.15	0.14	−0.10	−0.49	1.00			
7	Biotech	0.02	−0.17	0.00	−0.03	−0.63	−0.37	1.00		
8	Post Setback	0.27	0.05	0.19	0.01	−0.06	−0.03	0.09	1.00	
9	Listed	0.05	0.26	0.07	−0.01	.	0.49	−0.49	−0.02	1.00
	mean	0.46	2.06	32,314	66.90	0.46	0.22	0.32	0.41	0.62
	sd	1.35	3.68	3997	8.71	0.50	0.42	0.47	0.49	0.49
	min	0.00	0.00	7718	50.00	0.00	0.00	0.00	0.00	0.00
	max	23.00	39.00	50,002	90.00	1.00	1.00	1.00	1.00	1.00
	1998–2005	1	2	3	4	5	6	7	8	9
1	Patents GT	1.00								
2	Patent History	0.59	1.00							
3	Per Capita GDP	0.09	0.12	1.00						
4	Capital Fluidity	0.04	0.04	0.29	1.00					
5	PRO	0.00	−0.03	−0.18	−0.02	1.00				
6	Incumbent	0.05	0.11	0.00	−0.17	−0.34	1.00			
7	Biotech	−0.03	−0.05	0.18	0.13	−0.79	−0.31	1.00		
8	Post Setback	−0.02	0.07	0.14	0.09	−0.04	−0.02	0.05	1.00	
9	Listed	0.15	0.22	0.03	−0.15	.	0.47	−0.46	−0.01	1
	mean	0.82	2.25	36,938	67.58	0.46	0.12	0.42	0.40	0.46
	sd	2.05	5.88	7724	11.40	0.50	0.32	0.49	0.49	0.50
	min	0.00	0.00	525	30.00	0.00	0.00	0.00	0.00	0.00
	max	30.00	85	79,494	90.00	1.00	1.00	1.00	1.00	1.00

Table 2
Summary statistics industry participants in mAbs during mAbs setbacks sample (1988–1995) and GT setbacks sample (1998–2005).

	1988–1995	1	2	3	4	5	6	7	8	9
1	Patents mAbs	1.00								
2	Patent History	0.52	1.00							
3	Per Capita GDP	0.05	0.10	1.00						
4	Capital Fluidity	−0.01	0.01	0.31	1.00					
5	PRO	−0.05	−0.02	−0.06	0.29	1.00				
6	Incumbent	0.16	0.18	0.02	−0.33	−0.47	1.00			
7	Biotech	−0.10	−0.14	0.04	0.01	−0.58	−0.44	1.00		
8	Post-Setbacks	−0.09	0.02	0.16	0.01	−0.02	−0.02	0.04	1.00	
9	Listed	0.16	0.22	0.11	−0.22	.	0.53	−0.53	0.02	1.00
	mean	0.67	1.50	31,313	63.76	0.38	0.26	0.35	0.39	0.56
	sd	1.46	2.92	4859	10.45	0.49	0.44	0.48	0.49	0.50
	min	0.00	0.00	375	30.00	0.00	0.00	0.00	0.00	0.00
	max	27.00	39.00	58,101	90.00	1.00	1.00	1.00	1.00	1.00
	1998–2005	1	2	3	4	5	6	7	8	9
1	Patents mAbs	1.00								
2	Patent History	0.60	1.00							
3	Per Capita GDP	0.10	0.11	1.00						
4	Capital Fluidity	0.03	0.05	0.31	1.00					
5	PRO	−0.06	0.03	−0.12	0.05	1.00				
6	Incumbent	0.11	0.10	−0.03	−0.21	−0.34	1.00			
7	Biotech	−0.02	−0.10	0.14	0.10	−0.74	−0.39	1.00		
8	Post-Setbacks	0.06	0.07	0.14	0.09	−0.04	−0.02	0.05	1.00	
9	Listed	0.16	0.22	0.00	−0.17	.	0.50	−0.50	−0.03	1.00
	mean	0.63	2.36	36,946	66.46	0.39	0.15	0.46	0.40	0.47
	sd	1.60	6.10	7796	11.89	0.49	0.36	0.50	0.49	0.50
	min	0.00	0.00	525	30.00	0.00	0.00	0.00	0.00	0.00
	max	30.00	85.00	79,494	90.00	1.00	1.00	1.00	1.00	1.00

expected significant effect of the *Post-Setbacks* indicator on R&D efforts for both mAbs and GT. The estimated coefficient for *Post-Setbacks* is negative and significant for mAbs' R&D efforts in Model 1 (−0.28) and for GT R&D efforts in Model 4 (−0.11), while it is positive and significant for GT R&D efforts in Model 2 and mAbs R&D efforts in Model 3. These findings provide evidence that industry participants significantly reduced their R&D efforts following setbacks in the emerging technology, while they increased investments in the technology that had experienced progress. To better understand the magnitude of decline in R&D efforts following the setbacks, we can interpret the *Post-Setbacks* coefficient in Model 1 and 4 through exponentiation, which gives us the predicted change in the count of patenting following setbacks. For mAbs (Model 1), the expected count of mAb patenting following setbacks is only 0.76 times the count of mAb patenting in the

Table 3
Fixed effects quasi maximum likelihood Poisson regression estimates.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
	mAbs Setbacks sample (1988–1995)		GT Setbacks sample (1998–2005)		mAbs Setbacks sample (1988–1995)		GT Setbacks sample (1998–2005)		mAbs Setbacks sample (1988–1995)		GT Setbacks sample (1998–2005)	
Dependent Variable	Efforts mAbs	Efforts GT	Efforts mAbs	Efforts GT	Efforts mAbs	Efforts GT	Efforts mAbs	Efforts GT	Efforts mAbs	Efforts GT	Efforts mAbs	Efforts GT
Patent History	−0.00	−0.03	0.01***	0.01***	−0.00	−0.03	0.01***	0.01***	−0.01	−0.03	0.01***	0.01***
	(0.01)	(0.03)	(0.00)	(0.00)	(0.01)	(0.02)	(0.00)	(0.00)	(0.01)	(0.02)	(0.00)	(0.00)
Capital Fluidity			−0.00	−0.00			−0.01	0.00			−0.00	−0.00
			(0.01)	(0.01)			(0.01)	(0.01)			(0.01)	(0.01)
Per Capita GDP	−0.00***	0.00***	0.00***	0.00	−0.00***	0.00***	0.00***	0.00	−0.00***	0.00***	0.00***	0.00
	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)
Post-Setbacks	−0.28***	1.22***	0.11	−0.11**	−0.13	2.25*	−0.54*	0.73**	−0.15	1.10***	0.14*	0.14**
(1993–95 mAbs, 2003–05, GT)	(0.07)	(0.21)	(0.07)	(0.06)	(0.39)	(1.15)	(0.29)	(0.28)	(0.11)	(0.25)	(0.08)	(0.07)
Post-Setbacks					−0.01	−0.02	0.01**	−0.01***				
X Capital Fluidity					(0.01)	(0.02)	(0.00)	(0.00)				
Post-Setbacks									−0.25**	1.07***	0.08	−0.40***
X Incumbent									(0.13)	(0.41)	(0.12)	(0.12)
Post-Setbacks									−0.01	−0.33	−0.11	−0.48***
X Biotech									(0.17)	(0.32)	(0.10)	(0.10)
Firm Fixed Effects	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Observations	4818	2073	7933	8705	4818	2073	7933	8705	4818	2073	7933	8705
Number of assignees	647	288	1130	1291	647	288	1130	1291	646	288	1130	1291
Log likelihood	−3431	−1033	−5079	−6700	−3431	−1032	−5073	−6685	−3400	−1018	−5075	−6656
Chi-square	38.38	180.6	65.36	66.21	39.43	186.1	70.98	78.14	39.07	216	78.70	78.93

	(13)	(14)	(15)	(16)	(17)	(18)	(19)	(20)	(21)	(22)	(23)	(24)
	mAbs Setbacks sample (1988–1995)		GT Setbacks sample (1998–2005)		mAbs Setbacks sample (1988–1995)		GT Setbacks sample (1998–2005)		GT Setbacks sample (1998–2005)		GT Setbacks sample (1998–2005)	
Dependent Variable	Efforts mAbs	Efforts GT	Efforts mAbs	Efforts GT	Efforts mAbs	Efforts GT	Efforts mAbs	Efforts GT	Efforts GT	Efforts GT	Efforts GT	Efforts GT
Patent History	−0.01	−0.01	0.01***	0.01***	−0.00	−0.03	0.01***	0.01***	0.01***	0.02***	0.01***	0.02***
	(0.01)	(0.01)	(0.00)	(0.00)	(0.01)	(0.02)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)
Capital Fluidity			0.01**	0.00			−0.01	0.00	0.00	0.00	0.00	−0.00
			(0.01)	(0.00)			(0.01)	(0.01)	(0.01)	(0.00)	(0.01)	(0.01)
Per Capita GDP	−0.00**	0.00***	0.00***	−0.00	−0.00***	0.00***	0.00***	0.00	0.00	−0.00*	0.00	−0.00
	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)
Post-Setbacks	−0.13	0.59***	−0.18**	−0.06	0.15	2.06**	−0.57*	1.03***	1.02***	−0.08	1.17***	0.00
(1993–95 mAbs, 2003–05, GT)	(0.16)	(0.22)	(0.08)	(0.07)	(0.42)	(0.98)	(0.32)	(0.26)	(0.28)	(0.08)	(0.29)	(0.10)
Post-Setbacks					−0.01	−0.01	0.01**	−0.01***	−0.01***		−0.02***	
X Capital Fluidity					(0.01)	(0.01)	(0.00)	(0.00)	(0.00)		(0.00)	
Post-Setbacks					−0.23*	1.05**	0.10	−0.39***	−0.41***		−0.38***	
X Incumbent					(0.14)	(0.41)	(0.12)	(0.12)	(0.15)		(0.12)	
Post-Setbacks					−0.01	−0.41	−0.13	−0.47***	−0.42***		−0.40***	
X Biotech					(0.18)	(0.32)	(0.10)	(0.10)	(0.11)		(0.13)	
Listed	0.43	−0.17	−0.18	0.38***						0.18		0.19
	(0.34)	(0.33)	(0.18)	(0.11)						(0.12)		(0.14)
Post-Setback	−0.31*	0.81***	0.39***	−0.30***						−0.19**		−0.27**
X Listed	(0.18)	(0.26)	(0.08)	(0.08)						(0.09)		(0.11)
Firm Fixed Effects	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Observations	2962	1121	4834	4597	4818	2073	7933	8705	8031	3915	5838	1930
Number of assignees	415	169	740	776	647	288	1130	1291	1191	710	829	314
Log likelihood	−2218	−526.1	−3259	−3709	−3428	−1018	−5068	−6642	−5617	−2994	−4998	−2075
Chi-square	36.87	192.9	131.1	181.8	44.17	224.3	83.28	86.27	84.90	71.84	81.55	136.2

Robust standard errors in parentheses, *** $p < 0.01$, ** $p < 0.05$, * $p < 0.1$, Investment Climate (Capital Fluidity) does not change for the period 1988–1995. Post setbacks indicator is one for the years 1993–1995 (mAbs setbacks sample) and 2003–2005 (GT setbacks sample). PRO indicator is the baseline and not reported.

previous period. In a similar vein, the coefficient of *Post-Setbacks* in Model 4 suggests that the predicted count of GT patenting following setbacks is 0.89 times the count in the previous period.

In Models 5 to 8, we interact *Capital Fluidity* with the *Post-Setbacks* indicator. The interaction effects are not statistically different from 0 for the period involving mAbs setbacks (Models 5 and 6). This could be due to the fact that most of the R&D efforts for mAbs during that period were taking place in the US, limiting variation in the data in terms of differences in capital fluidity, and that there was a reasonably quick positive update in the US around mAbs with the FDA approval of ReoPro in 1994.[20] However, for the period involving GT setbacks, the interaction term is negative and statistically significant for GT R&D efforts (Model 8). This result suggests that the decline in GT R&D efforts following setbacks is much more pronounced in environments

[20] Excluding the US industry participants does not change our results for the effect of capital fluidity.

characterized by high capital fluidity. In exploring the interaction effects, we find that the estimate of the interaction term is driven by *Capital Fluidity* having a significant negative effect on GT R&D efforts following setbacks. We find no effect of *Capital Fluidity* on GT R&D efforts in the previous period. At high levels of *Capital Fluidity* (1 standard deviation above the mean) the predicated rate of GT patenting following setbacks is only 0.75 times the count of patents in the previous period, whereas at lower levels of *Capital Fluidity* (i.e. 1 standard deviation below the mean) the predicated rate of GT patenting following setbacks actually increases to 1.1 times the count of patents in the previous period.[21] In contrast, the interaction of *Capital Fluidity* with *Post-Setbacks* is positive and statistically significant for mAbs R&D efforts (Model 7) during the same period. This suggests that high capital fluidity can be associated with increased R&D efforts during periods of progress in a technology.

In Models 9 to 12, we interact the type of industry participant (*PROs, Biotechnology Entrant, Pharmaceutical Firm*) with the *Post-Setbacks* indicator. PROs are the omitted baseline category. The interaction effect for *Pharmaceutical Firm* with *Post-Setbacks* is negative and statistically significant for both mAbs (Model 9) and GT R&D efforts (Model 12). For *Biotechnology Entrants*, we observe this interaction effect to be negative and statistically significant for the GT R&D efforts (Model 12), whereas it is negative but not statistically significant for the mAbs R&D efforts (Model 9). The lack of statistical support for the decline in mAbs R&D efforts by biotechnology entrants could be due to the fact that many of these entrants were working on alternative mAbs solutions (e.g., humanized mAbs), which were not directly impacted by the setback. In exploring the interaction effects further, we find that the estimate in Model 9 is driven by a decline in mAbs R&D efforts by incumbent pharmaceutical firms following setbacks, whereas there is no statistically significant change in R&D efforts for both PROs and biotechnology entrants. For GT (Model 12), we observe that PROs show a significant increase in R&D efforts following the period of setbacks but biotechnology entrants and established pharmaceutical firms significantly decreased their R&D efforts. These analyses suggest that PROs are more likely than other industry participants to sustain their R &D efforts following setbacks.

In Models 13 to 16, we interact *Listed* with *Post-Setbacks* for firms in the sample and exclude PROs from the analysis. The interaction effect is negative and statistically significant for both mAbs (Model 13) and GT R&D efforts (Model 16). We find the opposite effect on R&D efforts for the alternative technology, which did not experience setbacks (Model 14 and 15). These findings suggest that firms listed on the stock market tend to aggressively invest in emerging technologies during progress but also curtail their R&D efforts to a much greater degree in the face of setbacks. For both mAbs (Models 13) and GT (Model 16), we observe that the estimates are driven by a significant decline in R&D efforts by publicly listed firms following a period of setbacks. Conversely, the change for the privately financed firms following setbacks is negative but not statistically significant. Models 17 to 20 are estimated using the full sample with the interaction terms for both the institutional environment and the type of industry participant, showing very similar results to the ones discussed above.

While we took a number of steps to ensure the reliability of the patent-based sampling for gene therapy, we undertook additional analyses to establish the robustness of our findings. First, to rule out the possibility that some of our findings may be an artefact of the Human Genome Project during the mid-1990s and early 2000s, we identified 80 assignees (i.e., firms and PROs) in our sample who were actively involved in this initiative.[22] Excluding these organizations from the sample did not change the patterns of our results (Models 21–22). Second, we explored whether our findings for the biotechnology entrants are not driven by those "pure-play" entrants who are only pursuing upstream research, with little involvement in downstream development and commercialization. Similar to prior studies (Hopkins et al., 2013), we limited our analysis to include only the 174 biotechnology entrants who were active in GT development, as captured by the Pharmaprojects and Adis R&D Insights drug development databases (Models 23–24). The results continue to be very similar to the main sample. Also, as previously discussed, patents assigned to gene therapy code in Derwent may be much broader in terms of their claims and may only be peripherally related to gene therapy. While we attempted to address this issue when constructing the patent-based sample, we performed another check in the statistical analysis by excluding all patents associated with gene therapy that are assigned to a broad set of Derwent codes. Specifically, we used a one standard deviation above the mean number of codes as a threshold for a given patent's exclusion. The findings with respect to post-setbacks GT R&D efforts continued to exhibit patterns similar to the main sample. Relatedly, to ensure that there are no systematic differences in the types of gene therapy patents between the pre- and the post-setbacks periods, we compared the distribution of the most frequently utilized codes within the set of focal patents and found them to be qualitatively similar.

To ensure that our results are not driven by industry participants located in the United States, we checked whether the interactions with the *Post-Setbacks* indicator hold when excluding those participants from the analysis. The results from this sample are qualitatively similar as the main results. Further, including a US-specific indicator variable, and estimating its interaction with *Post-Setbacks* variable does not change the previously reported patterns. For GT, the interaction term is negative and statistically significant, suggesting that the decline in R&D efforts for US-based participants was more pronounced following the period of GT setbacks, even when accounting for capital fluidity.

A final robustness test was done to use an alternative measure for capital fluidity, capturing an indicator from the Venture Capital and Private Equity Country Attractiveness Index, which focuses on the effectiveness of capital markets and institutions in the country. The indicator centers on the presence of formal institutions supporting such the flow of capital into a country and ultimately correlates with the extent of venture capital activity in a country (Groh et al., 2013). Using this variable, the results are very similar to the main results using data from the Index of Economic Freedom. Also, using a country's GDP per capita measure as an additional interaction variable does not change patterns of our results with respect to capital fluidity.

6. Discussion

The emergence of new technologies holds great promise for society. However, the process of emergence does not often adhere to a smooth pattern of cumulative progress but is instead punctuated by episodes of setbacks (Kline and Rosenberg, 1986; Nelson, 1964). Industry participants and capital providers pursuing an emerging technology in the hope of successful commercialization face the important choice as to whether to continue investing in the emerging technology in the face of setbacks or to withdraw and reallocate capital to alternative opportunities. This response has significant implications, not only for the industry participants themselves, but also for the overall evolution of the technology. We explore how this response to setbacks may vary across industry participants having different motivations and under differing

[21] The predicted effects are based on other covariates at their mean value and relying on the assumption that the fixed effects are zero.

[22] The source for identifying the organizations was the "Human Genome Project Documentary History: An Annotated Scholarly Guide to the HGP." The development of this guide was sponsored by the National Library of Medicine (NLM) in the US and the guide includes a list of organizations involved in the project.

degrees of pressure from their capital providers (Ferreira et al., 2014; Hopkins et al., 2013; Nelson, 1986; Salter and Martin, 2001) and who may be embedded in institutional environments with different levels of capital fluidity (Bartholomew, 1997; Brown et al., 2009; Kaiser and Prange, 2004; Li and Zahra, 2012). In so doing, we highlight that organizational and institutional characteristics typically attributed to facilitating the pursuit of emerging technologies do indeed induce greater levels of R&D efforts during periods of progress, but that those same characteristics are also associated with a greater decline in R&D efforts following periods of setbacks.

The context for the study is the global pharmaceutical industry and we contrast industry participants' pursuit of two of the most promising biotechnologies that emerged in the late 1980s — gene therapy (GT) and monoclonal antibodies (mAbs). Both technologies experienced episodes of progress and setbacks, albeit at different points in time. We observe that a multitude of different industry participants embedded in different institutional environments invested in the technology. However, following the period of setbacks, we typically see a pattern of reduced R&D efforts by these participants. Among the different types of organizations, the decline was more pronounced for pharmaceutical firms than for PROs for both GT and mAbs and for biotechnology entrants in contrast to PROs for GT. We also find that the reduction in R&D efforts was greater for those that were listed on the stock market than for those that were privately financed. Finally, when faced with setbacks in GT, industry participants in countries with higher capital fluidity more readily reduced their R&D efforts as compared to those located in countries where capital fluidity was more constrained. In many cases, these patterns of industry participants` R&D efforts in the face of setbacks are the opposite of the patterns seen during periods of progress. For example, as compared to privately-financed firms, publicly-listed firms expended significantly more R&D efforts during periods of progress, whereas they were also the ones to expend significantly less R&D efforts in the face of setbacks. Similarly, as compared to PROs, pharmaceutical incumbents expended greater R&D efforts during periods of progress, whereas they were also the ones to expend significantly less R&D efforts in the face of setbacks.

Our findings show that explicitly considering setbacks as a key feature in the evolution of emerging technologies can yield valuable insights regarding how industry participants react to technological setbacks, and how those setbacks may shape the industry participants' distribution of R&D efforts towards technological advance. We demonstrate that institutional and organizational factors typically considered to be positive enablers of cumulative technological advance can actually have a negative effect in the face of setbacks. In terms of institutional factors, the ease of capital flows is often assumed to be a positive feature of the institutional environment with respect to the pursuit of emerging technologies (Bartholomew, 1997; Beck et al., 2000; Lerner and Tåg, 2013). However, such an environment also provides valves through which investors and firms can shift resources away from emerging technologies suffering from setbacks. It is interesting to note that, following a setback, a more constrained institutional environment with respect to capital flows, one that is associated with less developed institutions and capital markets, may actually provide a stabilizing effect to sustain R&D efforts, at least in the short-term. This finding has important implications for the literature on how national innovation systems can facilitate or hinder progress in emerging technologies (Godoe, 2000; Kaiser and Prange, 2004).

In terms of organizational factors, the literature has shown biotechnology entrants and even incumbent pharmaceutical firms as fueling the development and commercialization of emerging technologies (Deeds et al., 2000; Jiang et al., 2011; Rothaermel, 2001). Yet, these firms significantly reduced their R&D efforts in the face of setbacks in GT and pharmaceutical firms significantly reduced their R&D efforts in the face of setbacks in mAbs. While they may be motivated and possess the necessary complementary assets to pursue emerging technologies, they are also subject to external pressures from their resource providers and internal organizational processes, which may make it more difficult to sustain their R&D efforts in the face of a setback. The fact that firms listed on the stock markets reduced their R&D efforts substantially more than did those who were privately financed illustrates how these challenges are amplified in the context of institutional capital markets (Aggarwal and Hsu, 2013; Ferreira et al., 2014). Thus, while firms can tap into capital markets to finance innovation and have seen to enjoy benefits in achieving R&D-related outcomes (Hopkins et al., 2013), being listed on the stock market may also lead to external pressures and short-term scrutiny following setbacks, curtailing their R&D efforts in the emerging technology.

Our study also expands on the role of PROs in the evolution of emerging technologies. Prior studies have emphasized the initial originating role of PROs in the context of emerging technologies through novel discoveries and basic research (Cohen et al., 2002; Zucker et al., 1998). We demonstrate that, in the face of setbacks, PROs may also play a crucial sustaining role. In so doing, we also illustrate that, when setbacks are encountered, there is a notable shift in the industry`s locus of innovation away from pharmaceutical firms and new biotechnology entrants and towards PROs.

Overall, these findings have important implications for policymakers in terms of policies designed to promote free flow of capital and to fund public research. While high capital fluidity may enhance the innovativeness of their regions with respect to emerging technologies, it also carries the risk of rapid capital outflows in the face of technological setbacks. Policymakers could mitigate the effect of setbacks on their regions' innovativeness by continuing to support public research that may be critical in resolving the unanticipated challenges in emerging technologies. Additionally, policy makers could encourage greater cooperation between firms and PROs, especially during periods of setbacks. For example, in the case of gene therapy, many incumbent pharmaceutical firms have benefitted from their partnerships with public research organizations in moving the commercialization of gene therapy forward (e.g., Novartis with the University of Pennsylvania).

Finally, our study deploys a new methodology that leverages archival textual data from scientific journals and the popular press to evaluate historical trends in the positive and negative sentiments towards an emerging technology. Thus, we show that sentiment analysis could offer a useful methodological approach for scholars studying the evolution of an emerging technologies and, perhaps more importantly, help identify periods and events that cause a significant shift in the overall sentiments. Scholars studying emerging technologies have drawn on several sources of data such as patents, a technology's performance attributes, and its market adoption, to study patterns of investments and improvements in that technology. Sentiment analysis could add to this repertoire of data and methods to explore research questions around the evolution of technology and could be especially valuable when technology is in a nascent stage of emergence and data with respect to that technology's performance and market share may not be readily available.

The study has a number of limitations, which should present ample opportunities for future research. It is carried out in the context of a single industry, and while we perform a detailed comparison of two technologies that emerged at the same time, the generalizability of our findings and their boundary conditions need to be established through explorations of other technologies in different industry contexts. Also, while many of the patterns discussed hold for both mAbs and GT, we are unable to completely explore the technological differences between mAbs and GT that may impact some of the divergent patterns. Future work could also examine the role of patent disputes and that of intellectual property rights more broadly in impacting progress in an emerging technology. For example, GenPharm, a promising mAbs entrant, faced patent litigation at a critical time of its evolution, impacting its ability to commercialize mAbs (Marks, 2015). In a similar vein, new forms of gene editing (e.g., CRISPR) with significant therapeutic potential have been contested in the courts, which may delay their

emergence.

Although our approach of using data on patent grants to evaluate the pattern of investment in GT and mAbs is consistent with prior research, the correlation between R&D efforts and patenting may vary across organizations, and over time. Hence, our inferences with respect to R&D efforts may not hold across all organizations that invested in GT and mAbs. Along the same lines, our analysis also precludes us from drawing inferences with respect to products in development resulting from the underlying patents, technology commercialization, and the economic gains that firms may derive from emerging technologies. Further, we note that the use of sentiment analysis for the purpose of studying emerging technologies may require extra care because positive and negative sentiments may have multiple causes, and we hope that future research can improve the methodology that we introduced in this paper.

Finally, our intent in this study is not to suggest that the reduction in R&D efforts following the setback in an emerging technology is an undesirable path of action. It is possible that the challenges underlying setbacks may be too significant to be resolved and yield a successful emergence of the new technology. In these cases, reducing efforts may indeed be a desirable option. However, a commonly observed scenario tends to be that emerging technologies that are subject to setbacks do successfully evolve over time, either in the intended industry domain, as was the case of semiconductor lithography (Kapoor and Adner, 2016), or in a new industry domain, as was the case of biogas (Geels and Raven, 2006). Technologies may also quickly recover their momentum, as was the case of mAbs. Such cases reinforce the important role played by PROs in technological advancement, and also may explain why those organizations that persisted with the emerging technology in the face of setbacks are more likely to reap the benefits from that technology's eventual fruition. In the case of gene therapy, many of the challenges that surfaced during the period of setbacks have been resolved. PROs have been at the forefront in the advance of these technologies and many therapy approvals have stemmed from their persistence towards gene therapy during the last decade (Kapoor et al., 2017). Future work could examine how different industry participants and participants embedded in different institutional contexts react to such a “re-emergence” in a technology.

In conclusion, we hope that the study offers an important perspective on technology emergence that incorporates both progress and setbacks into the technology's evolution. We use this perspective to show how institutional environments and organizational factors may impact the response of different types of actors to setbacks, and to offer implications for policy. In so doing, the study illustrates how setbacks can reconfigure the locus of innovation in emerging technologies and allows us to offer a richer perspective on technology emergence as one that is rooted in both progress and setbacks.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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